IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of	
MOON HAE SUNWOO, et al.	
Serial No.: 09/853,761	Examiner SHEIKH
Filed: May 14, 2001	Group Art Unit 1615
For: DEMINERALIZED CORTICOCANCELLOUS BONE SHEET	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF

STATEMENT

This Brief is filed in support of the Applicant's appeal of the Examiner's Final Rejection dated March 14, 2003 rejecting Claims 1-37. The Final Rejection was in response to Applicant's First Amendment of December 17, 2002. An Amendment to the Final Rejection, Request for Extension of Time and Notice of Appeal was timely filed on September 15, 2003, which Amendment was entered by an Advisory Action dated October 15, 2003.

REAL PARTY IN INTEREST

The party named in the caption of the brief is the lead inventor. All inventors are

employees of the Musculoskeletal Transplant Foundation. The application has been assigned to Musculoskeletal Transplant Foundation, a District of Columbia not for profit corporation.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Applicant which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

Claims 1-3, 5-9, 11-14, 27-31, 34, 36 and 37 stand finally rejected under 35 U.S.C. 103(a) as being unpatentable in view of Boyce U.S. Patent Number 5,899,939 and claims 4, 10, 15-26, 32, 33 and 35 stand finally rejected under 35 U.S.C. 103(a) as being unpatentable in view of Boyce et al. '939 when combined with and in view of Boyce et al. U.S. Patent Number 6,294,187. Claims 1 and 4 have been rejected under the judicially created doctrine of double patenting in view of Claims 1 and 10 of U.S. Patent Number 6,326,018.

Claims 1-5 and 7-37 are being appealed.

STATUS OF THE AMENDMENTS

The Examiner issued a final rejection on March 14, 2003 rejecting the claims. An Amendment, Request for Extension of Time and Notice Appeal was made after the final rejection presenting arguments as to why the references were not valid prior art. This Amendment was considered and entered by the Examiner but not felt by the Examiner to

place the case in condition for allowance.

SUMMARY OF THE INVENTION

The present invention is directed towards a flexible, single piece demineralized unitary bone sheet 10 formed from a tubular bone member 20 which is cut 22 along its longitudinal axis. The resultant bone sheet is comprised of cortical cancellous bone having a cortical section 12, a cortical cancellous bone interface section 13 and a cancellous section 14. The bone sheet 10, after the demineralization, has a residual calcium weight of about 3.0% to about 8.0% to which a hyaluronic acid component having a molecular weight of 700,000 to 1,500,000 is added, with the weight of the component ranging from 1% to about 5% of the total sheet weight. The bone sheet after demineralization is flexible and is adapted for use in the vivo repair of a mammalian or animal skeletal system with the thickness of the treated cortical cancellous sheet ranging from 2.0mm to about 8.0mm. The bone sheet has sufficient flexibility to allow the sheet to be shaped to conform to the configuration of a skeletal region to be repaired and sufficient tensile strength to allow the sheet to be so shaped without damage to the sheet.

ISSUES PRESENTED

(1) Whether the invention as defined in Claims 1-3, 5, 7-9, 11-14, 27-31, 34, 36 and 37 is obvious and therefore unpatentable under 35 U.S.C. 103(a) over the cited prior art reference to Boyce et al. U.S. Patent Number 5,899,939.

(2) Whether the invention as defined in claims 4, 10, 16-26, 32, 33 and 35 is obvious

and therefore unpatentable under 35 U.S.C. 103(a) over the cited prior art references of Boyce '939 combined with Boyce et al. 6,294,187.

(3) Whether the invention as defined in claims 1 and 4 should be rejected under the judicially created doctrine of double patenting over claims 1 and 10 of U.S. Patent Number 6,326,018 B1.

GROUPING OF THE CLAIMS

The grouping of the Claims 1-5 and 7-33 (Group 1) is directed toward a sterile flexible one piece bone sheet for use during the in vivo replacement or reformation of preselected portions of an animal skeletal system. The bone sheet comprises a continuous integral unitary sheet of demineralized natural bone with a cortical layer and a cancellous layer with the cortical layer interfacing with the cancellous layer through a cortical cancellous section. The thickness of the bone sheet ranges from 2.0mm to 8.0mm with the sheet being capable of being bent from its original shape to conform to the configuration of a skeletal region to be repaired without damage to the sheet and is capable of inducing osteogenesis at the skeletal region.

The grouping of Claims 34-37 (Group 2) is directed toward a method of making a bone sheet with cortical and cancellous portions from a tubular bone portions using the entire bone portion as the bone sheet.

ARGUMENT

I. **Applicant traverses the Examiner's rejection of claims 1-3, 5-9, 11-14, 27-**

31, 34, 36 amd 37 as obvious amd therefore unpatentable under 35 U.S.C. 103(a) over the cited prior art reference to Boyce et al. U.S. Patent Number 5,899,939.

The present invention is a bone sheet taken from a singular tubular bone under the method claimed in claim 34 using all of the cortical, cortical cancellous interface, and cancellous portions of the tubular bone which naturally occur to form the one piece unitary bone sheet. The bone sheet is partially demineralized, leaving a single integral sheet composed of integral sections having different structural and osteoinductive qualities having a residual calcium content of a specified range of from about 3% to about 8%. Previously, it had been believed that the cancellous layer portion of a bone could not be used in a structural device and bone sheets were taken from cortical bone, demineralized and then glued or fastened with mechanical fasteners together. Since there is a shortage of human donors it is imperative that allograft donor bone be used as efficiently as possible. The present invention thus provides for a more efficient use of natural existing human bone to obtain maximum material use of a natural surgical implant material having a great demand but limited supply.

The Boyce et al '939 reference is a bone derived implant of a load bearing composite structure which is made up of at least two superimposed layers of fully mineralized or demineralized or partially demineralized cortical bone material adhesively secured or fastened to each other to form a single rigid structure which is then cut into shaped implants. At least one layer is a compression strength imparting layer derived from non demineralized cortical bone or cortical bone which has been partially demineralized. The implant structure is constructed after demineralization of some layers has been undertaken with no degree of

demineralization having been disclosed. The Boyce '939 implant is not made from a single piece of formed bone but from a composite of slices taken from a specific bone or bones from the same donor. While the Examiner has characterized Boyce '939 as comprising a unified structure of two or more layers which includes a demineralized cortical layer and another layer of a different material, (the patent actually notes this different material as fully demineralized bone or hydroxyapatite) this does not teach any of the layers to be cancellous or that the structure contains a cortical cancellous interface. The cited paragraphs of Boyce '939 do not teach the present invention. The implant of Boyce et al. '939 is described as noted on Column 5 lines 62-65, "the cortical portion of bone 10 taken from the diaphyseal region is cut into cortical bone layers 11 of varying width by slicing the bone longitudinally". Thus only cortical bone is used with the cancellous and cortical cancellous being wasted or subjected to granulation. These layers are optionally demineralized. The Boyce '939 composite structure, can be anywhere from 2 to 200 layers overall preferably adhesively secured together, with a layer thickness ranging from about 0.5 to about 20 mm. A specific overall compression strength for the implant ranging from about 25 to about 250 Mpa, preferably 100 to about 200 Mpa can be obtained. The separate control layers of Boyce et al. '939 are held together through the use of biological compatible adhesives and mechanical fasteners such as pins, screws, dowels quite unlike the present invention which requires no adhesive or fasteners and makes maximum use of human bone. Thus, the present invention does not have the problem of layer shearing or separation or the problem of securing the mechanical fasteners in the layered product which are subjected to the various stresses which occur on the implant when the same is used in a human. Figure 2 of Boyce et al. '939

illustrates an implant comprising alternating layers of fully mineralized cortical bone and partially demineralized cortical bone. There is no discussion of the amount of demineralization and layers are fully mineralized to keep the compression strength of the implant. Example 1 of Boyce et al. '939 is directed toward slices of mineralized bone and Example 2 is directed toward half of the slices being fully demineralized. As noted in Examples 1 and 2, the slices are held together with cyanoacrylate adhesive. Example 3 is directed to longitudinally cut fully mineralized bars arranged in a lattice structure. In short all that this reference teaches is the assembly of layers of cut cortical bone which are adhesively held together to provide a layered assembly which is then cut into the desired shape. This does not approach or begin to teach the present invention. The Boyce et al. '939 reference teaches away from the present invention.

Furthermore, Boyce et al. '939 does not teach residual calcium left after demineralization because the bone is fully demineralized to achieve osteoinductiveness. The Examiner's response that routine or manipulative experimentation could obtain the ranges of residual calcium are without merit. Technical studies have shown that residual calcium has a benefit in the bone healing process.

There is no teaching in Boyce et al. '939 of the claimed method. See Figure 1 of Boyce et al. '939 for the slicing of the bone pieces and Figure 2 for the stacking of the assembly as well as Examples 1-3 of same.

The present invention is a simple solution to solve a complex problem of maximum usage of human allograft bone tissue. To maintain that combining cortical bone layers in a sandwich or stacked construction using adhesive or mechanical fasteners to hold the same

together for use as a shaped implant to render the present invention obvious is an example of hindsight combined with supposition, not a teaching of obviousness.

Applicants would thus submit that the cited reference does not teach or obviate the present invention. There is no teaching of the cancellous and cortical layers and no teaching of the cancellous cortical interface section. There is also no teaching of the method claimed or of steps which would obviate the claimed method.

II. Applicant traverses the Examiner's rejection of claims 4, 10, 16-26, 32, 33 and 35 is obvious and therefore unpatentable under 35 U.S.C. 103(a) over Boyce et al. 6,294,187.

As previously noted the Boyce et al '939 reference is a bone derived implant of a load bearing composite structure which is made up of at least two superimposed layers of fully mineralized or demineralized or partially demineralized cortical bone material adhesively secured or fastened to each other to form a single rigid structure which is then cut into shaped implants. The implant structure is constructed after demineralization has been undertaken with no degree of demineralization having been disclosed. The Boyce '939 implant is not made from a single piece of formed bone but from a composite of slices taken from the control layer. The cited paragraphs of Boyce '939 do not teach the present invention. The implant of Boyce et al. '939 is described as noted on Column 5 lines 62-65, "the cortical portion of bone 10 taken from the diaphyseal region is cut into cortical bone layers 11 of varying width by slicing the bone longitudinally". Thus only cortical bone is used with the cancellous and cortical cancellous being wasted or subjected to granulation. These layers are optionally demineralized. The Boyce '939 composite structure, can be anywhere from 2 to

200 layers overall and are adhesively secured together, with a thickness ranging from about 0.5 to about 20 mm and a noted compressive strength. The separate control layers of Boyce et al. '939 are held together through the use of biological compatible adhesives and mechanical fasteners such as pins, screws, dowels quite unlike the present invention which requires no adhesive or fasteners and makes maximum use of human bone. Thus, the present invention does not have the problem of layer shearing or separation or the problem of securing the mechanical fasteners in the layered product which are subjected to the various stresses which occur on the implant when the same is used in a human. Figure 2 of Boyce et al. '939 illustrates an implant comprising alternating layers of fully mineralized cortical bone and partially demineralized cortical bone. There is no discussion of the amount of demineralization and layers are fully mineralized to keep the compression strength of the implant. Example 1 of Boyce et al. '939 is directed toward slices of mineralized bone and Example 2 is directed toward half of the slices being fully demineralized. As noted in Examples 1 and 2, the slices are held together with cyanoacrylate adhesive. Example 3 is directed to longitudinally cut fully mineralized bars arranged in a lattice structure. In short all that this reference teaches is the assembly of layers of cut cortical bone which are adhesively held together to provide a layered assembly which is then cut into the desired shape. This does not approach or begin to teach the present invention. The Boyce et al. '939 reference teaches away from the present invention.

Furthermore, Boyce et al. '939 does not teach residual calcium left after demineralization because the bone is fully demineralized to achieve osteoinductiveness. The Examiner's response that routine or manipulative experimentation could obtain the ranges of

residual calcium are without merit. Published technical studies have shown that residual calcium has a benefit in the bone healing process.

The Boyce '187 patent simply teaches a rigid osteoimplant bone composition formed of shaped compressed bone particles having a bulk density of greater than about $0.7/g/cm^3$. These powdered bone particles range in average particle size from about 0.05 to about 1.2 cm in size and are obtained by milling or shaving the surface of an entire bone with at least 60% of the bone particles being elongated. Preferably at least 60% and most preferably at least about 90% by weight of the bone particles are elongate. The particles possess an average median length to median thickness ratio of from about 1:1 to about 3:1. Particles are formed by milling whole bone to produce fibers, chipping whole bone, chipping whole bone, cutting whole bone, fracturing whole bone in liquid nitrogen or otherwise disintegrating the bone tissue. The bone particles employed in the composition can also be obtained from cortical, cancellous and/or corticocancellous bone. Preferably, the bone particles are obtained from cortical bone of allogenic origin. Compressive forces of about 2,500 to 60,000 psi preferably ranging from 4 to about 72 hours in addition to heating are applied to the bone particles in a mold to produce a "hard chalk-like material" (Col. 11, ln.66). The osteoimplant can then be lyophilized and crosslinked. There is no teaching using the natural layer of cancellous bone or cortical cancellous interface as part of a bone sheet in a continuous integral sheet of bone used for surgical repair. Indeed, the prevailing view was that only cortical bone could be used for strength reasons. However, it has been found that cancellous bone can be used and that it has excellent osteoinductive properties. The '187 reference does not teach or suggest the present invention which has a continuous sheet of demineralized bone

with a cortical and cancellous layer taken from a single bone.

Applicants would thus submit that the cited references in combination do not teach or obviate the present invention. There is no teaching of the cancellous and cortical layers and no teaching of the cancellous cortical interface section, indeed there is only an inferential mention that particles having such composition can be used. One cannot combine references, one of which uses a sandwich construction of layers of cut cortical bone held together with adhesive or fasteners with an implant formed of elongate ground particles held together by the use of high compressive forces and heat to arrive at the present invention except through hind site and conjecture. Obviousness must be based on what is shown in the prior art. There is also no teaching of the method claimed nor could one possible combine the two references, slicing of cortical bone and adhesively fixing the layers together of Boyce et al. '939 and the slurry and compression of particles of Boyce et al. '187 to arrive at the claimed method.

III. Applicant traverses the Examiner's rejection of claims 1 and 4 under the judicially created doctrine of double patenting over claims 1 and 10 of U.S. Patent Number 6,326,018 B1.

The Examiner's has rejected claims 1 and 4 of the present invention as double patenting in view of claims 1 and 10 of U.S. Patent Number 6,326,018 B1. The '018 patent is directed toward a totally different invention. Claim 1 of the '018 patent reads as follows:

> **1. A sterile flexible sheet of allograft bone for application to a bone defect site comprising a high molecular weight cross linked hydrogel selected from a group consisting of hyaluronic acid and chitosan having a molecular weight of at least 500,000 Daltons in a water solution with a concentration of demineralized human bone particles ranging from about 25% to about 50% by weight, the demineralized bone particles ranging in size from about 250 to ab ut 850 microns in size, said concentration being lyophilized to rem ve the water component of said**

solution leaving behind a flexible static sheet of bone particles suspended in the dehydrated hydrogel matrix. (Emphasis added)

A double patenting rejection of the obvious type is analogous to the non obviousness requirement of 35 U.S.C. 103 in that no person of ordinary skill in the art would conclude that the invention defined in the claims in issue is an obvious variation of the invention defined in the claims of the '018 patent. However only the claims are compared and not the whole document as would be required in a normal 35 U. S. C. 103 rejection.

The '018 patent is comprised of small demineralized bone particles ranging in size from 250 to about 850 microns and a carrier which is lyophilized to remove the water component leaving a flexible static sheet of bone particles in contrast to the present invention which uses a tubular piece of allograft bone. The sheet of the '018 patent is quickly dissolved and broken apart by the patients blood after the same has been implanted. There is no teaching of a unitary structure taken from a piece of tubular bone having integral cortical, cortical cancellous and cancellous layers or the thickness of such layers. Indeed there are no layers or section in the sheet of the '018 patent, only a mass of particles bound together. The bone content of the '018 patent ranges from 25% to 50% by weight while the present invention is formed from whole bone with a 95% plus bone content. There is no lyophilization required to remove the water content of the present invention. There is no obviousness rejection which should be applied to this claim.

Claim 10 is simply directed to a sheet made of bone powder which is cortiocancellous. Claim 10 reads as follows:

10. A sterile flexible sheet of demineralized bone as claimed in claim 1 wherein said bone powder is corticocancellous.

Likewise, no obviousness rejection should be applied to this claim.

Each double patenting situation must be decided on its own facts. The basic question to be asked is does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the cited patent. The answer is no. Claims 1 and 10 do not teach, obviate, or suggest claims 1 and 4 of the present invention and do not represent a viable obviousness double patenting rejection. The fact that a patent may be in the same field of endeavor and may contain similar components is not a basis for a double patenting rejection.

A copy of the 6,326,018 patent is attached hereto as Exhibit 1 for the Board's review.

SUMMARY OF ARGUMENT

The respective grounds of final rejection of the claims of this application under 35 U.S.C. 103(a) and claims 1 and 4 under obviousness double patenting are incorrect for the reasons advanced above. Reversal thereof by the Honorable Board of Patent Appeals and Interferences is therefore requested and is earnestly solicited.

Our check in the amount of $330.00 is attached to cover the cost of filing this Brief and two copies. Oral hearing will be requested during the rebuttal time period. If any additional fees are incurred, kindly charge the same to our Deposit Account No. 07-1340.

Respectfully submitted,

GIPPLE & HALE

John S. Hale
Registration No. 25,209

(703) 448-1770
6665-A Old Dominion Drive
McLean, Virginia 22101
Attorney Ref.: X-9338

9. A sterile flexible bone sheet according to claim 1 wherein said demineralized bone sheet has an osmolality ranging from 290mmol/kg to 310mmol/kg.

10. A sterile flexible bone sheet according to claim 1 wherein said cortical cancellous bone sheet comprises from 99% to 95% by weight of the demineralized bone and from 1% to 5% by weight from a group consisting of hyaluronic acid, sodium hyaluronate and derivations thereof.

11. A sterile flexible bone sheet according to claim 1 wherein said cortical cancellous bone sheet is cut from tibial allograft tissue.

12. A sterile flexible bone sheet according to claim 1 wherein said cortical cancellous bone sheet is cut from femoral allograft tissue.

13. A sterile flexible bone sheet according to claim 1 wherein said cortical cancellous bone sheet is cut from pelvic allograft tissue.

14. A sterile flexible bone sheet according to claim 1 wherein said cortical cancellous bone sheet is cut from cancaneal allograft tissue.

15. A sterile flexible bone sheet for use during the in vivo replacement or reformation of preselected portions of a human bone comprising a continuous unitary sheet of demineralized natural bone including a cortical layer portion which interfaces with a cancellous layer portion with the thickness of said bone sheet ranging from 2.0mm to 6.0mm, said sheet having hyaluronic acid or derivatives thereof with a molecular weight over 700,000 Daltons added thereto at a concentration of 1.0 to 4.0 mg/ml, said sheet being flexible for application to a bone to be repaired without damage to the sheet, said sheet being capable of inducing osteogenesis at the bone region.

16. A sterile flexible bone sheet according to claim 15 wherein the thickness of

said cortical portion ranges from 1mm to 3mm and the thickness of said cancellous portion ranges from 1mm to 3mm.

17. A sterile flexible bone sheet according to claim 15 wherein said demineralized sheet has residual calcium ranging from 3.0% to 8.0% by weight of the demineralized bone mass.

18. A sterile flexible bone sheet according to claim 15 wherein said demineralized sheet has a neutral pH.

19. A sterile flexible bone sheet according to claim 15 wherein said demineralized bone sheet has an osmolality ranging from 290mmol/kg to 310mmol/kg.

20. A sterile flexible bone sheet according to claim 15 wherein said demineralized bone sheet comprises from 99% to 95% by weight of the demineralized cortical cancellous bone.

21. A sterile flexible bone sheet according to claim 15 wherein said cortical layer interfaces with said cancellous layer through a cortical cancellous section.

22. A sterile flexible bone sheet according to claim 15 wherein said cortical cancellous bone sheet is cut from tibial allograft tissue.

23. A sterile flexible bone sheet according to claim 15 wherein said cortical cancellous bone sheet is cut from femoral allograft tissue.

24. A sterile flexible bone sheet according to claim 15 wherein said cortical cancellous bone sheet is cut from pelvic allograft tissue.

25. A sterile flexible bone sheet according to claim 15 wherein said cortical cancellous bone sheet is cut from cancaneal allograft tissue.

26. A sterile flexible bone sheet according to claim 15 wherein said sheet has a

width and length ranging from 1-20cm.

27. A sterile flexible bone sheet for use during the in vivo replacement or reformation of preselected portions of a human bone comprising a continuous unitary sheet of demineralized natural bone with a cortical layer and a cancellous layer with a cortical/cancellous interface , the thickness of said sheet comprising a cortical layer ranging in thickness from 1mm to 3mm and a cancellous layer ranging in thickness from 1mm to 3mm, the sheet being capable of being bent from its original shape to conform to the configuration of a bone to be repaired without damage to the sheet, said sheet being capable of inducing osteogenesis at the bone region.

28. A sterile flexible bone sheet according to claim 27 wherein said cortical cancellous bone sheet is cut from tibial allograft tissue.

29. A sterile flexible bone sheet according to claim 27 wherein said cortical cancellous bone sheet is cut from femoral allograft tissue.

30. A sterile flexible bone sheet according to claim 27 wherein said cortical cancellous bone sheet is cut from pelvic allograft tissue.

31. A sterile flexible bone sheet according to claim 27 wherein said cortical cancellous bone sheet is cut from cancaneal allograft tissue.

32. A sterile flexible bone sheet for use during the in vivo replacement or reformation of preselected portions of an animal skeletal system comprising of a continuous unitary sheet of demineralized natural bone with a cortical layer and a cancellous layer with a cortical cancellous interface, said demineralized bone having a residual calcium weight ranging from 3.0% to 8.0% by weight of the demineralized bone mass with the thickness of said sheet ranging from 2.0mm to 8.0mm, said sheet containing buffered hyaluronic acid or

a derivative of same with a molecular weight over 700,000 Daltons and having a neutral pH, the bone sheet being capable of being bent from its original shape to conform to the configuration of bone to be repaired without damage to the sheet, said sheet being capable of inducing osteogenesis at the bone region.

33. A sterile flexible bone sheet for use during the in vivo replacement or reformation of preselected portions of a human bone comprising a continuous unitary sheet of demineralized natural bone with a cortical layer, a cancellous layer and a cortical cancellous interface said demineralized natural bone having a residual calcium ranging from 3.0% to 8.0% by weight of the demineralized bone mass with the thickness of said sheet ranging from 2.0mm to 6.0mm, said sheet containing therein, a hydrogel taken from a group consisting of hyaluronic acid, sodium hyaluronate or derivatives thereof with a molecular weight over 700,000 Daltons and having a neutral pH with an osmolality of 290mmol/kg to 300mmol/kg, the sheet being capable of being bent from its original shape to conform to the configuration of a bone to be repaired without damage to the sheet, said sheet being capable of inducing osteogenesis at said bone to be repaired.

34. A method of making a bone sheet with cortical and cancellous portions comprising:

a). cutting a human bone into substantially tubular portions;

b). cleaning marrow, blood and lipids from said tubular cut human bone;

c). cutting said cleaned tubular bone longitudinally along its length;

d). demineralizing said cut tubular bone rendering the same flexible; and

e). pulling the ends of said bone formed by said longitudinal cut apart to form a bone sheet with cortical and cancellous portions.

35. A sterile flexible bone sheet according to claim 34 including the step of adding 1% to 5% hyaluronic acid by weight to the bone sheet.

36. A sterile flexible bone sheet according to claim 34 wherein said sheet is demineralized to have residual calcium ranging from 3.0% to 8.0% by weight of the demineralized bone mass.

37. A sterile flexible bone sheet according to claim 34 wherein said demineralized sheet has a neutral pH.